# CSF amyloid $\beta$ 1-42 predicts cognitive decline in Parkinson disease

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## ABSTRACT

**Objective:** Cognitive decline associated with Parkinson disease (PD) is common and highly disabling. Biomarkers that help identify patients at risk for cognitive decline would be useful additions to the clinical management of the disease.

**Methods:** A total of 45 patients with PD were enrolled in this prospective cohort study and had at least 1 yearly longitudinal follow-up evaluation. CSF was collected at baseline and cognition was assessed at baseline and follow-up visits using the Mattis Dementia Rating Scale (DRS-2). CSF was tested for amyloid $\beta$ 1-42 ($A\beta_{1\text{-}42}$), p-tau$_{181p}$, and total tau levels using the Luminex xMAP platform. Mixed linear models were used to test for associations between baseline CSF biomarker levels and change in cognition over time.

**Results:** Lower baseline CSF $A\beta_{1\text{-}42}$ was associated with more rapid cognitive decline. Subjects with CSF $A\beta_{1\text{-}42}$ levels ≤192 pg/mL declined an average of 5.85 (95% confidence interval 2.11–9.58, $p = 0.002$) points per year more rapidly on the DRS-2 than subjects above that cutoff, after adjustment for age, disease duration, and baseline cognitive status. CSF total tau and p-tau$_{181p}$ levels were not significantly associated with cognitive decline.

**Conclusions:** Reduced CSF $A\beta_{1\text{-}42}$ was an independent predictor of cognitive decline in patients with PD. This observation is consistent with previous research showing that Alzheimer disease pathology contributes to cognitive impairment in PD. This biomarker may provide clinically useful prognostic information, particularly if combined with other risk factors for cognitive impairment in PD. ***Neurology*® 2010;75:1055–1061**

## GLOSSARY

**AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **CI** = confidence interval; **DLB** = dementia with Lewy bodies; **DRS-2** = Dementia Rating Scale (version 2); **H&Y** = Hoehn & Yahr; **PD** = Parkinson disease; **PDD** = Parkinson disease dementia.

Cognitive impairment is common in Parkinson disease (PD), with dementia occurring in up to 80% of patients over the course of their illness.[1] When dementia is present, it worsens disability,[2] results in greater caregiver burden,[3] and increases mortality.[4] Clinical features including older age, male sex, lack of tremor, greater postural instability, and subtle impairments on cognitive tests are risk factors for more severe cognitive impairment and progression to PD dementia (PDD).[5,6]

In addition to these clinical features, biomarkers could potentially improve the ability to predict risk for cognitive impairment and PDD. Among currently available candidate biomarkers, CSF measures of Alzheimer disease (AD) pathology including $A\beta_{1\text{-}42}$, tau, and p-tau$_{181p}$ have attractive properties including validated assessment methods[7] and relevance to putative components of the underlying pathology in PDD and dementia with Lewy bodies (DLB).[8] Both CSF $A\beta_{1\text{-}42}$ and tau

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levels have been associated with impaired cognition in cross-sectional studies of patients with PD and DLB.[9,10] In the present longitudinal study, we tested whether CSF $A\beta_{1\text{-}42}$, tau, and p-$tau_{181p}$ could predict risk of subsequent cognitive decline in patients with PD. We hypothesized that subjects with biomarker profiles similar to those seen in patients with AD would show the greatest cognitive decline.

## METHODS

**Subjects.** Patients aged 60 or older with a diagnosis of PD based on British Brain Bank criteria[11] and a range of cognitive function were recruited to the University of Pennsylvania Udall Center for this study from the Parkinson's Disease and Movement Disorders Center at University of Pennsylvania. No subjects met criteria for DLB.[12] A total of 45 subjects contributed spinal fluid samples and had at least one yearly follow-up visit, and were therefore eligible for this analysis.

**Standard protocol approvals, registrations, and consents.** The study was approved by the University of Pennsylvania Institutional Review Board. Informed consent was obtained prior to administration of any study procedure.

**Assessments.** The clinical and neuropsychological evaluation was administered by trained research staff. Demographic and general clinical information was collected in PD-DOC recommended format (http://www.pd-doc.org). Evaluations were conducted between August 2006 and December 2009.

***Neuropsychological assessment.*** Cognitive status was assessed using the Mattis Dementia Rating Scale (version 2) (DRS-2).[13] The DRS-2 is a detailed measure of general cognitive ability. It contains subscales that measure specific cognitive domains: memory, attention, initiation/perseveration, construction, and conceptualization. It has been validated in patients with PD,[14] and a cutoff score of ≤123 has been shown to accurately identify patients with PDD.[15] The same study reported a mean DRS score of 133 for patients with PD without dementia.

***Motor examination.*** Clinical examinations, including Hoehn & Yahr (H&Y) staging,[16] were conducted by the patients' treating doctors who are movement disorders specialists. Motor examinations were conducted while patients were receiving their regularly scheduled dopaminergic medications.

***CSF analysis.*** CSF samples were obtained by lumbar puncture using a 20- or 24-gauge spinal needle as described in the Alzheimer's Disease Neuroimaging Initiative (ADNI) procedures manual (http://www.adni-info.org/). CSF was divided into aliquots (0.5 mL) and stored in bar code–labeled polypropylene vials at −80°C. $A\beta 1\text{-}42_{1\text{-}42}$, tau, and p-$tau_{181p}$ were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA AlzBio3; Ghent, Belgium; for research use only reagents) immunoassay kit–based reagents. Full details for this combination of immunoassay reagents and analytical platform are provided elsewhere.[17] Reliability studies (http://www.adni-info.org) show that the day-to-day reproducibility for these 3 biomarkers varies by less than 10%.

**APOE *genotyping.*** DNA was extracted from EDTA blood samples using commercial reagents (FlexiGene, Qiagen, Valencia, CA). DNA was available for 43 of the 45 participants. Two single nucleotide polymorphisms (rs7412 and rs429358) in *APOE* were genotyped using allelic discrimination assays with TaqMan reagents (Applied Biosystems, Foster City, CA) on an ABI7500. The *APOE* genotypes (ϵ2, ϵ3, and ϵ4) were assigned by incorporating the genotyping results from both single nucleotide polymorphisms into an algorithm.

**Analysis.** Descriptive statistics for clinical and CSF variables ($A\beta_{1\text{-}42}$, tau, p-$tau_{181p}$, and their ratios: tau/$A\beta_{1\text{-}42}$ and p-$tau_{181p}$/$A\beta_{1\text{-}42}$) were calculated. Linear mixed-effects models were used to test for associations between baseline CSF biomarkers and cognitive decline as measured by the DRS-2.[18] A linear mixed-effect model accounts for within-person correlations over time, and allows for variable length of follow-up between subjects. These models can also accommodate varying time intervals between assessments. Each subject in this mixed-effect model can be thought of as having his or her own linear regression model, and the population parameters can be obtained by averaging across the individual regression coefficients. In our implementation, the intercept and the regression coefficients for the follow-up time were treated as random effects such that each subject has a unique intercept and regression coefficient for the follow-up time. The population mean coefficients for the follow-up time were obtained by averaging across the subject-specific regression coefficients for the follow-up time. This population mean coefficient estimated the average annual change for the DRS-2 over time, and accounts for differences in baseline DRS-2 scores. The interaction term time × CSF biomarker represents the effect of the baseline biomarker on change in DRS-2 score over time. It can be interpreted as the annualized change in DRS-2 score for each one unit change in a given biomarker. In addition to considering $A\beta_{1\text{-}42}$, tau, and p-$tau_{181p}$ as continuous measures, we also examined the effect of being at or below the $A\beta_{1\text{-}42}$ cutoff of 192 pg/mL. This level has been associated with the greatest diagnostic accuracy in separating patients with AD from age-matched controls.[7] In this case, the time × $A\beta_{1\text{-}42}$ group interaction can be interpreted as the between-group difference in annualized rate of DRS-2 decline. Analogous tests were performed for subscales of the DRS-2.

Potential confounding variables including age, gender, education, H&Y stage, and disease duration were tested in bivariable analysis. Only age, H&Y stage, and disease duration were associated with DRS-2 score below the $p < 0.1$ cutoff, and were included in subsequent models. With the exception of *APOE* genotype, complete data were available for 45 subjects. *APOE* status was available for 42 of 45 subjects, and the association between *APOE* ϵ4 carrier status and cognitive decline was tested in this subset of subjects.

All analyses were conducted at a 2-sided $\alpha = 0.05$ significance level, without adjustment for multiple comparisons. Analyses were carried out using Stata version 10 (College Station, TX).

## RESULTS

**Subject characteristics and cognitive status.** At the time of this analysis, 45 subjects had at least 1 yearly follow-up clinical evaluation, 20 had 2 follow-up evaluations, and 3 were evaluated 3 years after baseline. None have been lost to follow-up or withdrawn consent. For the entire cohort, the annualized rate of decline in DRS-2 was 3.4 points (±0.96). Baseline demographic characteristics are shown in table 1.

**Association between CSF biomarkers and baseline cognitive status.** We found no association between CSF biomarkers and baseline cognitive status (table 2). The result was the same with or without adjustment for covariates. At baseline, 6 subjects were below the

**Table 1** Baseline characteristics of 45 patients with Parkinson disease

| Characteristics | Values |
|---|---|
| Female, n (%) | 6 (13) |
| Age, y, mean (range, SD) | 73 (62–90, 7.8) |
| Baseline Dementia Rating Scale score, mean (SD) | 133 (9) |
| College education, n (%)[a] | 31 (68) |
| Disease duration at baseline, y, mean (range, SD) | 11 (3–27, 0.75) |
| Hoehn & Yahr stage, n (%) | |
| I | 6 (13) |
| II | 29 (64) |
| III | 9 (20) |
| IV–V | 1 (2) |
| *APOE* ϵ4 allele present, n (%)[b] | 15 (36) |
| $A\beta_{1\text{-}42}$ pg/mL, mean (range, SD) | 224 (78–380, 74) |
| Tau pg/mL, mean (range, SD) | 52 (10–154, 29) |
| p-$Tau_{181p}$, pg/mL, mean (range, SD) | 18 (4–57, 12) |
| Duration of follow-up, y, mean (SD) | 1.5 (1.2) |

[a] Subjects with at least partial college education compared to those never attending college.
[b] *APOE* genotype known in 42 of 45 subjects.

DRS-2 cutoff of 123 that is associated with a diagnosis of dementia.[15] There were no differences in biomarker values for these subjects compared to those with DRS-2 scores >123. For example, mean CSF $A\beta_{1\text{-}42}$ was 226 pg/mL (SD 77) in subjects with DRS-2 scores >123 and 210 pg/mL (SD 60) in subjects ≤123 ($p = 0.63$). However, the small number of subjects with low baseline DRS-2 scores limits our ability to make this comparison.

**Association between CSF biomarkers and longitudinal change in cognition.** Reduced CSF $A\beta_{1\text{-}42}$ was strongly associated with decline in cognitive function over time (table 2). Results were similar in unadjusted analysis ($\beta = 0.041$; 95% confidence interval [CI] 0.015 to 0.066), and with adjustment for age, disease duration, and baseline H&Y stage ($\beta = 0.040$; 95% CI 0.015 to 0.066). There was no association of either total tau or p-$tau_{181p}$ and greater cognitive decline. In addition, there was no association between tau/$A\beta_{1\text{-}42}$ and p-$tau_{181p}$/$A\beta_{1\text{-}42}$ ratios and change in cognition. This was true in spite of the strong relationship between $A\beta_{1\text{-}42}$ and cognitive decline. Adding tau or p-$tau_{181p}$ in a combined metric actually diminished the effect of $A\beta_{1\text{-}42}$ alone.

A CSF $A\beta_{1\text{-}42}$ level of ≤192 pg/mL has been suggested as a useful diagnostic cutoff for AD.[7] We tested whether subjects in our cohort with CSF $A\beta_{1\text{-}42}$ below this level were at greater risk for cognitive decline, and found that those with $A\beta_{1\text{-}42}$ levels ≤192 had an annualized decline in DRS score that was 6.1 points greater (95% CI 2.33 to 9.79) than those with $A\beta_{1\text{-}42}$ levels above 192 pg/mL. This association was quite similar after adjustment for age, disease duration, and baseline H&Y stage (5.8 points greater; 95% CI 2.11 to 9.58). After 2 years, the mean adjusted DRS-2 score for subjects with low baseline $A\beta_{1\text{-}42}$ levels had fallen below the published cutoff for dementia of 123 on the DRS-2, while the mean adjusted score for subjects with $A\beta_{1\text{-}42}$ levels above 192 remained above 130 (figure).

**Associations with *APOE* status.** Fifteen subjects carried at least one *APOE* ϵ4 allele (one subject was homozygous). CSF $A\beta_{1\text{-}42}$ levels were substantially lower in these subjects (182 pg/mL vs 251 pg/mL; $p = 0.004$). CSF tau and p-$tau_{181p}$ levels were not significantly different for *APOE* ϵ4 allele carriers compared to noncarriers (tau: 46 vs 55; $p = 0.35$; p-$tau_{181p}$: 18 vs 19; $p = 0.836$). Without adjustment for CSF $A\beta_{1\text{-}42}$, having at least one *APOE* ϵ4 copy was associated with an increase in the rate of cognitive decline compared to noncarriers that approached significance (difference = 3.96 DRS-2 points/year, 95% CI −0.39 to 8.32; $p = 0.075$). However, the association with of *APOE* ϵ4 allele status was no longer present after adjustment for CSF $A\beta_{1\text{-}42}$ level (difference = 1.29 points/year, 95% CI −3.15 to 5.73; $p = 0.569$). No other *APOE* genotypes were associated with cognitive decline (data not shown).

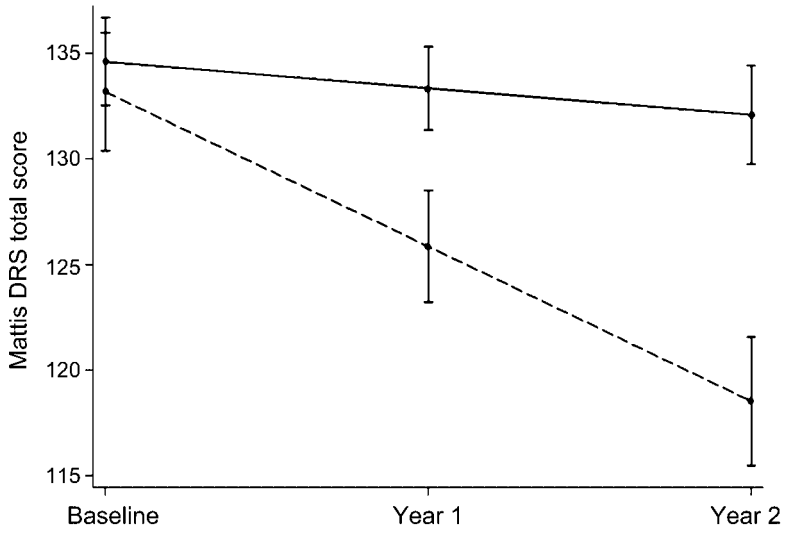
**Association between CSF biomarkers and change in individual cognitive domains.** Low CSF $A\beta_{1\text{-}42}$ was significantly ($p < 0.05$) associated with declines in multiple subscales of the DRS-2. The largest effect size was seen for the attention subscale ($\beta = 0.011$, SE = 0.0034). There were also significant associations with change in conceptualization ($\beta = 0.0078$, SE = 0.0033) and memory ($\beta = 0.0086$, SE =

**Table 2** CSF biomarkers as predictors of deterioration on the DRS-2[a]

| CSF biomarkers | Estimated association with baseline DRS-2 | | Estimated association with annual DRS-2 change | |
|---|---|---|---|---|
| $A\beta_{1\text{-}42}$ | −0.0038 (0.02) | $p = 0.835$ | 0.040 (0.013) | $p = 0.002$ |
| Tau | 0.008 (0.046) | $p = 0.857$ | −0.0031 (0.035) | $p = 0.928$ |
| p-$Tau_{181p}$ | 0.133 (0.11) | $p = 0.261$ | −0.069 (0.083) | $p = 0.401$ |
| Tau/$A\beta_{1\text{-}42}$ ratio | 1.23 (4.74) | $p = 0.797$ | −4.47 (3.70) | $p = 0.227$ |
| p-$Tau_{181p}$/$A\beta_{1\text{-}42}$ ratio | 16.86 (11.6) | $p = 0.154$ | −12.25 (7.85) | $p = 0.118$ |

Abbreviation: DRS-2 = Dementia Rating Scale (version 2).
[a] Data are shown as $\beta$ (SE). For the first column, each coefficient ($\beta$) represents the difference in baseline DRS-2 score per 1-point difference in biomarker. For the second column, coefficients represent the difference in annual rate of change of the DRS-2 for each 1-point change in the biomarker. For example, a subject with a baseline $A\beta_{1\text{-}42}$ level of 150 pg/mL might be expected to decline 4.0 points more rapidly per year on the DRS-2 than a subject with a baseline $A\beta_{1\text{-}42}$ level of 250 pg/mL. Estimates of rate of change are adjusted for age, Hoehn & Yahr, and disease duration.

**Figure** **Change over time in mean Dementia Rating Scale (version 2) (DRS-2) total score**




Change over time of the DRS-2 for subjects with CSF $A\beta_{1\text{-}42}$ levels above 192 pg/mL (solid line) compared to those with baseline $A\beta_{1\text{-}42}$ at or below 192 pg/mL (dashed line). Data shown are the mean predicted DRS-2 scores (±1 SE) based on output from a mixed linear model, adjusted for age, Hoehn & Yahr stage, and disease duration.

0.0042). The association with the initiation/perseveration subscale approached significance ($\beta$ = 0.011, SE = 0.0064, $p$ = 0.06). There was no significant association with the construction subscale. These findings suggest an association with global cognitive decline, rather than an association limited to one cognitive domain.

**DISCUSSION** Low baseline CSF $A\beta_{1\text{-}42}$ levels were a strong predictor of subsequent cognitive decline in this cohort of patients with PD. Neither tau nor p-$tau_{181p}$ was associated with cognitive decline, and ratios of p-$tau_{181p}$ and tau to $A\beta_{1\text{-}42}$ were no better predictors than $A\beta_{1\text{-}42}$ alone. The effects sizes we observed are likely to be clinically meaningful. Based on our data, a patient with CSF $A\beta_{1\text{-}42}$ below the diagnostic cutoff of 192 pg/mL would be predicted to progress from essentially normal cognition to a level consistent with PDD within a 2-year period of follow-up. Decline was observed across multiple cognitive domains, suggesting an anatomically generalized, rather than focal, degeneration.

We found no association between biomarker levels and baseline cognitive status, even after adjustment for disease duration. This may be due to a number of factors including the small number of patients with PD with a DRS-2 score in the dementia range (i.e., ≤123) or biases inherent in cross-sectional analyses. Our results are also consistent, however, with the hypothesis that biomarker abnormalities precede clinical cognitive decline.

Similar cross-sectional studies have not found a relationship between CSF $A\beta_{1\text{-}42}$ levels or plasma $A\beta$ levels and cognitive status in patients with AD.[19,20] However, recent studies have documented that reductions in CSF $A\beta_{1\text{-}42}$ are associated with risk of subsequent cognitive decline. In the ADNI cohort, lower CSF $A\beta_{1\text{-}42}$ levels (and elevated tau) were associated with increased risk of conversion from mild cognitive impairment to AD.[7] In another AD cohort, lower CSF $A\beta_{1\text{-}42}$ and elevated p-$tau_{181p}$ (to a greater extent than total tau) predicted more rapid cognitive decline.[21] Finally, a recent study showed that alterations in various $A\beta$ peptides in plasma were associated with risk of subsequent dementia.[22]

Lower levels of CSF amyloid-$\beta$ peptides, specifically $A\beta_{1\text{-}42}$, reflect underlying amyloid pathology.[23,24] Some have hypothesized that in AD, lower $A\beta_{1\text{-}42}$ levels in the spinal fluid may be related to sequestration of the peptide from CSF into amyloid plaques.[25] In Lewy body disorders, the picture is more complicated. Decreased levels of $A\beta_{1\text{-}42}$ have been demonstrated in CSF from patients with DLB compared to normal controls.[9,26] In patients with PDD, modest reductions in CSF $A\beta_{1\text{-}42}$ have been shown compared to normal controls,[27,28] and in PD without dementia, $A\beta_{1\text{-}42}$ levels are not consistently reduced.[9] Increased CSF levels of total tau and p-$tau_{181p}$ have been associated with impaired cognitive performance in patients with PD and PDD.[10] These differences in CSF $A\beta_{1\text{-}42}$ across the spectrum of Lewy body disorders may reflect a gradient in the relative contribution of amyloid pathology to DLB, PDD, and PD without dementia, respectively. Such a hypothesis is consistent with neuropathologic data showing that amyloid plaque pathology is common in DLB and present to a lesser degree in PDD.[29] If lower CSF $A\beta_{1\text{-}42}$ levels reflect greater amyloid plaque burden in patients with PD at risk for cognitive decline, then this in turn argues for an important role for amyloid pathology in the development of dementia in PD.

The presence of at least one *APOE* $\epsilon$4 allele is an established risk factor for amyloid aggregation and AD.[30] A meta-analysis of the published studies on the relationship between *APOE* genotype and risk of dementia in PD[31] found modestly increased risk associated with the $\epsilon$4 allele, and no definite associations with other alleles. We found a modest association that approached significance between *APOE* $\epsilon$4 carrier status and rate of cognitive decline, with carriers of at least one copy of the $\epsilon$4 allele having more rapid cognitive decline. However, this association was substantially smaller than the association with CSF $A\beta_{1\text{-}42}$, and was no longer significant after adjustment for CSF $A\beta_{1\text{-}42}$ level. Moreover, consistent

with previous studies,[32] baseline CSF $A\beta_{1-42}$ was significantly lower in subjects with at least one *APOE* $\epsilon 4$ allele. These findings argue that the *APOE4* genotype and $A\beta_{1-42}$ may function in the same pathway, but that CSF $A\beta_{1-42}$ is more directly related, and more predictive of cognitive decline in PD than *APOE* genotype. Interestingly, there is evidence that reduced CSF $A\beta_{1-42}$ may confer greater risk for conversion from mild cognitive impairment to AD in *APOE* $\epsilon 4$ noncarriers.[33] Studies with larger sample size and longitudinal design may help clarify the relationship between *APOE* $\epsilon 4$ status and other genetic traits such as tau haplotype[34] and dementia risk in PD.

Several limitations of our study should be acknowledged. First, we studied a relatively small sample of patients with PD and for a relatively brief period of time. As a result, we are not able to perform subgroup analyses, such as examining the association between CSF $A\beta_{1-42}$ and cognitive decline in men vs women or in recently diagnosed vs established cases of PD. We were able to detect an association of CSF $A\beta_{1-42}$ level with cognitive decline because the DRS-2 is a relatively precise, continuous measure of cognitive status, and because of the longitudinal design of our study. Our findings should be replicated in larger groups of patients, and in longer studies that examine the risk of conversion to a clinical diagnosis of PDD. Second, our results do not address whether the association between reduced $A\beta_{1-42}$ and cognitive decline is specific to PD. Similar declines in cognition have been observed in apparently healthy populations.[35] Our results may reflect the effects of the primary underlying pathologic process in PDD, or simply coexisting AD pathology that modifies CSF $A\beta_{1-42}$ levels and also may, in part, underlie cognitive impairment in PD. One means to address this issue would be to study additional CSF biomarkers. Recently, specific subtypes of amyloid peptides such as $A\beta_{1-40}$ have been shown to differentiate PDD from DLB and may be a more specific marker of cortical Lewy body pathology.[9] In addition, assays for $\alpha$-synuclein pathology are under development, and may be useful in determining prognosis in patients with PD.[36]

These limitations are opportunities for future research. Nonetheless, our study remains significant in that it demonstrates the ability of a CSF biomarker to provide prognostic information for patients with PD on the risk of cognitive decline. In the future, biological data such as CSF $A\beta_{1-42}$ level could be combined with clinical information that has been associated with risk of PDD to provide better predictive accuracy than either type of information alone.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## DISCLOSURE

Dr. Siderowf serves on a scientific advisory board for and has received speaker honoraria from Teva Pharmaceutical Industries Ltd.; serves/has served as a consultant to Supernus Pharmaceuticals, Inc., Teva Pharmaceutical Industries Ltd., Merck Serono, and Schering-Plough Corp.; receives research support from the NIH (NINDS U10 NS0444451 [site PI], NINDS P50 NS053488 [Co-I], NINDS R43NS0636071 [Co-I], and NINDS R01NS065087 [Co-I]), the US Department of Defense, and the Department of Health, Commonwealth of Pennsylvania; and has served as a consultant on manganese litigation. Dr. Xie receives research support from the NIH/NINDS (NS053488 [coinvestigator and core director]). Dr. Hurtig served on a grant review panel for the Michael J. Fox Foundation for Parkinson's Research; serves on the editorial board of *Parkinsonism and Related Disorders*; serves as Movement Disorders Section Editor for UpToDate; has received speaker honoraria from Teva Pharmaceutical Industries Ltd.; receives research support from Teva Pharmaceutical Industries Ltd., Boehringer Ingelheim, Bayer Schering Pharma, Kyowa Hakko Kirin Pharma, Inc., PRA International, Novartis, GlaxoSmithKline, Avid Radiopharmaceuticals, Inc., St Jude Medical, Amarin Corporation, Prestwick Pharmaceutical, Inc., HP Therapeutics Foundation, Inc., Cephalon, Inc., NIH (NINDS P50 NS053488-01 [core leader and PI] and NINDS U10 NS044451-023 [site PI]); and holds stock in Teva Pharmaceutical Industries Ltd. Dr. Weintraub has served on a scientific advisory board for Boehringer Ingelheim; serves on the editorial board of *Movement Disorders*; has received honoraria from Boehringer Ingelheim, ACADIA Pharmaceuticals Inc., GE Healthcare, Novartis, Osmotica Pharmaceutical Corp., BrainCells Inc., Merck Serono, Sanofi-Aventis, Johnson & Johnson, Solvay Pharmaceuticals, Inc., and Pfizer Inc.; and receives research support from Boehringer Ingelheim, the NIH (K23 MH067894 [PI]), the Penn Center for Excellence in Research on Neurodegenerative Diseases (CERND), and the Michael J. Fox Foundation for Parkinson's Research. Dr. Duda served on a grant review panel for the Michael J. Fox Foundation for Parkinson's Research; serves/has served on a scientific advisory boards for Boehringer Ingelheim, the Lewy Body Dementia Association, and the Lewy Body Society; has received honoraria for interviews for articles in the *PD Monitor and Commentary*, a publication supported by an educational grant from Teva Pharmaceutical Industries Ltd.; receives research support from the Department of Veterans Affairs (Biomedical Laboratory Research and Development Service Merit Award [PI], Cooperative Studies Program 468 [site PI]), the NIH (RO1 NS41265-01 [Co-I], RO1 NS44266 [Co-I]), the Michael J. Fox Foundation, the Department of Health, Commonwealth of Pennsylvania, and the Samueli Foundation; and holds stock in C.R. Bard, Inc., Celgene, Clarient, and Johnson & Johnson. Dr. Chen-Plotkin receives research support from the Burroughs Wellcome Fund and the NIH (K08 AG033101 [PI]). Dr. Shaw has served on a scientific advisory board for Bristol-Myers Squibb; has received funding for travel and speaker honoraria from Pfizer Inc.; serves on the editorial board of *Therapeutic Drug Monitoring*; may potentially receive revenue for patent pending re: O-methylated rapamycin derivatives for alleviation and inhibition of lymphoproliferative disorders, licensed by the University of Pennsylvania to Novartis; receives royalties from publication of *Applied Pharmacokinetics and Pharmacodynamics: Principles of Therapeutic Drug Monitoring* (Wolters Kluwer/Lippincott Williams & Wilkins, 2005); receives research support from the NIH (AG024904 [Co-PI Biomarker Core Laboratory] and 1RC 2AG-036535 (ARRA) [PI Biomarker Core Laboratory]); and receives board of directors' compensation and holds stock options in Saladax Biomedical. Dr. Van Deerlin serves on the editorial board of *Molecular Diagnosis and Therapy*; has a patent pending re: Compositions and methods for the treatment of frontotemporal lobar degeneration with TDP-43 inclusions; receives royalties from the publication of *Molecular Pathology in Clinical Practice* (Springer, 2007); and receives research sup-

port from the NIH (NS053488 [Neuropathology and Genetics Core, Core Co-Leader] and AG010124 [Neuropathology Core, Co-I]). Dr. Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd.; has received speaker honoraria from Pfizer Inc.; serves as an Associate Editor of *Alzheimer's & Dementia*; may accrue revenue on patents re: Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer's disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, Diagnostic methods for Alzheimer's disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody; and receives research support from the NIH (NIA P01 AG 09215-20 [PI], NIA P30 AG 10124-18 [PI], NIA PO1 AG 17586-10 [Project 4 Leader], NIA 1PO1 AG-19724-07 [Core C Leader], NIA 1 U01 AG 024904-05 [Co-PI Biomarker Core Laboratory], NINDS P50 NS053488-02 [PI], NIA UO1 AG029213-01 (Co-I); RC2NS069368 (PI), RC1AG035427 (PI), and NIA P30AG036468 [PI]) and the Marian S. Ware Alzheimer Program. Dr. Clark serves as Medical Director of and holds stock options in Avid Radiopharmaceuticals, Inc.; has served on scientific advisory boards for Elan Corporation and Wyeth; and receives research support from the Department of Health, Commonwealth of Pennsylvania.

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